STATE MEDICAID P&T COMMITTEE MEETING

FRIDAY, May 16, 2008
7:00 a.m. to 8:30 a.m.
Cannon Health Building
Room 125

MINUTES

Committee Members Present:

Kort DeLost, R.Ph. — **Karen Gunning, Pharm D.**
David Harris, M.D. — **Duane Parke, R.Ph.**
Raymond Ward, M.D. — **Jerome Wohleb, Pharm D.**

Board Members Excused:

Lowry Bushnell, M.D. — **Thomas Miller, M.D.**
Koby Taylor, Pharm D.

Dept. of Health/Div. of Health Care Financing Staff Present:

Lisa Hulbert — **RaeDell Ashley**
Jennifer Zeleny — **Tim Morley**

University of Utah Drug Information Center Staff Present:

Chris Beckwith, Pharm. D. — **Erin Fox, Pharm D.**

Other Individuals Present:

Tony Molchan, Abbott	Steven Zhang, Abbott	Steve Hill, Organon
Craig Boody, Lilly	Roy Linfield, Schering	Steve Hill, Schering
Scott Brown, Teva	John Ostrom, Teva	Erika Brumleve, GSK
Doug Ethel, GSK	Abril Atherton, U of U	Marty Daniels, Merck
Maria Papayoti, AstraZeneca	Trish McDaid-O'Neill, AstraZeneca	Linda Craig, AstraZeneca
Russell Frandsen, Fiscal Analyst	Camille Kerr, Allergan	Ann Lingard, Student - COP
Caitlin Oderda, U of U	Paula Wood, U of U	Leslie Jensen, U of U

Meeting conducted by: Raymnd Ward, M.D., Chairperson.

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1. Minutes for March were reviewed and approved. Duane Parke made a motion to approve the minutes. Kort DeLost seconded the motion. The motion passed with unanimous votes from Kort DeLost, Karen Gunning, David Harris, Duane Parke, Raymond Ward, and Jerome Wohleb.

2. DUR Board Update: There was no DUR Board update this month. Duane Parke addressed the Committee. The P&T Committee is not allowed to address certain drug classes. The

Attorney General's office has also instructed Medicaid to proceed slowly in implementing the PDL. When Medicaid enters into a contract, it is for a specific drug product rather than a portfolio agreement with the company. There are now 22 contracts signed and in place. Medicaid is now receiving secondary rebates. The program structure is in place, and is now running well. Medicaid and the State expresses gratitude for the P&T Committee's work.

3. Drug Classes for PDL Consideration: Duane Parke addressed the Committee. To prepare this list, Duane had reviewed the bid sheet from the SSDC purchasing group and created this list. It is sorted by opportunity for savings. The Committee was asked to review and either approve or disapprove. The Committee was reminded that mental health drugs cannot be considered at this time.

   Dr. Ward asked if some of the groups, such as antibiotics, could be considered at the same meeting. Dr. Beckwith felt that this was not possible, since the cephalosporins, for example, are a very large class with three separate sub-classes. The same issue is true for the quinolones. Karen Gunning did not know if it was even appropriate to have a PDL for those classes, because they are different from one another based on their spectrum.

   Duane Parke stated that many other states have PDLs for both quinolones and cephalosporins. The Committee said that they would prefer to address antibiotics later.

   Dr. Beckwith stated that she has checked on which classes have documents prepared by OHSU. Reviewing classes with documents prepared by OHSU will maximize the cost savings for Medicaid, since the Drug Information Service will not have to prepare as much original research. Dr. Beckwith recommended an order for P&T Class reviews based on the availability of OHSU research. The Drug Information Service can prepare documents on combination products to consider at the same time as the overall class is considered.

   Duane Parke added that the bid process for the SSDC is open this month, for the manufacturers' information.

   Dr. Beckwith stated that she would advise the Committee to approve the list that Duane prepared, and allow her and Duane to work out the order in which the drug classes are addressed.

   Dr. Wohleb asked if there are other high-spend drug classes that are not included on this list. Because mental health drugs are not eligible for PDL consideration, the list is comprehensive. There are other drug classes that can be considered, such as opthalmics, but the classes do not have high enough spending associated with them to justify bringing it to the P&T Committee due to the cost of the drug class review. Karen Gunning pointed out that over the long-term it may be justified.

   Dr. Wohleb moved to approve the list and allow Duane and the Drug Information Service to determine the order. Kort DeLost seconded the motion. The motion passed with unanimous votes from Kort DeLost, Karen Gunning, David Harris, Duane Parke, Raymond Ward, and Jerome Wohleb.

   Dr. Ward asked that an ordered list be presented at the next meeting for final approval.

4. Asthma Drugs - Inhaled Corticosteroids: Dr. Beckwith addressed the Committee. The main

document for review was prepared by the Oregon Evidence-Based Practice Center. It was completed in January 2006. There are 6 agents in this class that are currently available in the United States. They are beclomethasone, budesonide, flunisolide, fluticasone, mometasone, and triamcinolone. Sequesonide is also FDA approved and available for asthma as Aldesco from Nicomed, but the company does not currently have a marketing date for the product. It was approved over a year ago, and they do not have a current release date planned. This agent was not included in the review, and should not be considered for the PDL.

These agents are all approved for asthma. Although there are some differences in specific age range, they are all approved for pediatric use. They are not FDA approved for use in COPD; this is an off-label use, but it is recommended based on national disease treatment guidelines. The Oregon review used the national disease treatment guidelines to develop comparative dosing guides for these agents so they could determine equivalent dosing. They divided the agents into groups of low, medium, and high doses for each product. This was used in determining dosage equivalency in head-to-head clinical trials. These guidelines are based on expert opinion and years of clinical use of these products.

For these products the key clinical questions were, for outpatients with asthma or COPD do the inhaled corticosteroids differ ineffectiveness? For the purposes of this discussion, only the orally inhaled products are under consideration. The second key clinical question was, for adults with asthma or COPD, do the inhaled corticosteroids differ in safety or adverse effects? The third one, are there subgroups of patients based on demographics, age, racial groups, gender, other medications, comorbidities, or pregnancy for which one inhaled corticosteroid is more effective or associated with fewer adverse events than another? The fourth one was, are there device or dosing specific differences that lead to differences in adherence, persistence, effectiveness, tolerability, or patient preference for these products? As far as outcome measures, they did establish endpoints for the key clinical questions. For effectiveness and efficacy, they looked at symptom alleviation, such as number of asthma episodes, COPD exacerbations, days and nights with symptoms, quality of life, ability to participate in work, school, sports, or physical activity, emergency department/urgent medical care visits, hospitalizations, mortality, and pulmonary function as measured by FEV1or PFR for COPD patients. For safety and tolerability, they only evaluated endpoints of overall adverse effects, withdrawals due to adverse effects, serious adverse effects, and specific adverse effects or withdrawals due to some specific cause related to corticosteroids, such as osteoporosis, growth retardation, acute adrenal crisis, cataracts, ocular hypertension, and open angle glaucoma.

The process for conduction this review was to search Medline, Cochran, Mbase, IPA, and the FDA's database. They also contacted the manufacturers for each product. These searches located a total of 1286 articles. They reviewed these abstracts and retrieved 432 articles that evaluated the endpoints of interest for the key clinical questions. Of these, 78 trials were included in this document.

For the first key clinical question of comparative efficacy in outpatients with asthma, there were no trials that compared all the agents at once. They had to look at specific comparisons between two agents. They did not report specific rates of hospital admission, beta agonist use, and other things like that. There are not a lot of hard numbers for that. Overall, they judged that the products are equal, have equivalent efficacy when given at equivalent doses. When it comes to health-related quality of life, there are few head-to-head trials. However, in the ones that were available, beclomethasone and fluticasone were equally effective.

Fluticasone was at least as effective as budesonide in two trials that evaluated quality of life. Fluticasone was somewhat more effective than triamcinolone in the one trial that evaluated quality of life. It is somewhat difficult to make a larger judgement about quality of life due to the limited amount of data. When they evaluated placebo-controlled trials, becolmethasone, budesonide, fluticasone, and mometasone all improved quality of life compared to placebo. For the second part of the key clinical question, which is comparative efficacy in patients with COPD, there are no head-to-head clinical trials. Overall, the inhaled corticosteroids do not decrease mortality. There are mixed results as to whether they reduce exacerbations, improve quality of life, or slow the decline of pulmonary function. In trials comparing them with placebo, there were actually several systematic reviews included. Two found that the inhaled corticosteroids were more effective than placebo, and one found that they had similar efficacy to placebo in reducing exacerbations and decline in FEV1.

They second key question, for adults with asthma or COPD, do the inhaled corticosteroids differ in safety or adverse events? There are no trials that reported differences in discontinuation rates due to adverse events. Overall, many of the head-to-head trials did not report adverse events or did not make comparisons on those endpoints. Of the 24 trials that did, 20 found no differences in the agents in adverse event rates. 4 of them did find some differences. 2 found that sore throat was more common with fluticasone than beclomethasone, 1 found that oral candidaisis was more common with fluticasone than triamcinolone, and 1 found that upper respiratory infection was more common with triamcinolone than with beclomethasone. Whether those are clinically significant effects are unclear. One long-term trial evaluated patients using inhaled corticosteroids for up to 3 years. When budesonide was evaluated compared to placebo in this study, the overall rate of upper respiratory infection was 38 % for both groups, the rate of oral candidaisis was about 1% with budesonide and ½% with placebo, and the discontinuation rates were equivalent in both groups. For effects on specific adverse events, they evaluated bone density and osteoporosis. Pooled results from two systematic reviews found that there were no effects from inhaled corticosteroids in patients with asthma or COPD on either bone mineral density or fractures. Of the individual trials that were included in this, there were 6 that included fracture rate, 3 of those 6 found a higher risk with inhaled corticosteroids, although that still appears to be a question that is up in the air. One head-to-head trial followed patients that were treated with beclomethasone, budesonide, or placebo for up to 2 years, and they found no difference between those agents and their effect on bone mineral density or fractures. The next specific adverse event that they looked as was growth retardation. In two head-to-head trials, there was a smaller decrease in growth velocity with fluticasone than with beclomethasone or budesonide, so there may be some small differences in the effect of these agents on growth velocity. When compared to placebo, there is a decrease in growth velocity in children receiving beclomethasone or budesonide. There is equivalent growth velocity in children receiving fluticasone or placebo. The long-term effects of these are unclear. There have been two cohort studies that evaluated children for 3-9 years. They found no effect on height at the end of that study between children that were treated with inhaled corticosteroids and children that were not. That was specifically with budesonide; the others have not been evaluated in the long-term. For acute adrenal crisis, there are no studies that evaluate comparative risk. It is known to be a possibility with all of the inhaled corticosteroids. Steroids have been known to increase the risk for cataracts. The question that was evaluated was whether the inhaled corticosteroids increase the risk for cataracts and if there are differences. There are no head to head trials. In one randomized controlled clinical trial, the risk was similar between budesonide and placebo. In two observational trials in children, risk was similar between budesonide and placebo. In 4

observational studies with adults over 40, the risk of cataracts did increase with the use of inhaled corticosteroids, and it was related to the dose that the patients received, age, and duration of therapy. With ocular hypertension, there are no head-to-head trials. Similar to the effect on cataracts, the increased risk is related to dose, and it is primarily seen in adults over 49.

The third key question are there subgroups of patients based on demographics, age, racial groups, gender, other medications, comorbidities, or pregnancy for which one inhaled corticosteroid is more effective or associated with fewer adverse events than another? None of the included studies were designed to specifically evaluate this. There is very little data available. To summarize, looking at patients in different age subgroups, the available evidence suggests that inhaled corticosteroids do not differ in efficacy and tolerability in pediatric or elderly patients as compared to the general adult population. For the subgroups of ethnicity, gender, comorbidities, or pregnancy there is insufficient evidence that any one agent is better than another. Similarly, with patients that are treated with other medications, all of these agents interact with cytochrome P450 3A4 inhibitors, so there is no difference there.

Finally, the question from the addendum, are there device or dosing specific differences that lead to differences in adherence, persistence, effectiveness, tolerability, or patient preference for these products? They went through the studies that they located in their searches, and they looked at the studies that were specifically assessing relationships between administration device or puffs per day that the patient needs to take, and how it impacted these measures. For the device related measures, there was one meta-analysis of 4 trials. They found that patient tended to prefer dried powder inhalers to metered dose inhalers. When the reviewers did this assessment, they looked only at if the same drug was given by two different devices. Two randomized controlled trials also evaluated this in adults. One found that patients prefer metered dose inhalers to dry powder inhalers, and the other found that dry powder inhaler was preferred over metered dose inhaler. There was a third randomized trial in children that compared nebulizer versus metered dose inhaler. Parents preferred nebulizer over metered dose inhaler, and compliance and adherence with the nebulizer were higher. For the dosing regimen question, there were no trials that could be included since many of the trials included were double dummy. There was, however, one systematic review that assessed differences in efficacy between once and twice daily dosing of beclomethasone, budesonide, flunisolide, fluticasone, and mometasone. The efficacy of twice daily dosing was generally superior to once daily dosing. However, the majority of the patients could be controlled with once daily dosing.

Overall, this document for this class of drugs suggests that there is no one agent or device that is more effective or safer for this class of drugs.

The Drug Information Service prepared a list of available agents to make sure that it was up to date. They also wanted to address some questions that have come up. There are no generics available for this class of drugs. There are some differences between these agents in whether they have a dose counter or if the patient is able to count remaining doses. It is not likely that these agents will have generics available for several years. These agents have all had to be reformulated to have an HFA propellant, and they have new patents. The Committee was also provided with equivalent dosing tables.

Roy Linfield from Schering Plough addressed the Committee. The Committee is asked to

place the Asmanex Twistinhaler on the PDL based on its unsurpassed clinical efficacy, safety, and ease of use. According to the NHL treatment guidelines, inhaled corticosteroids are the first line of treatment for mild to moderate persistent asthmatic agents. Combination agents, such as Advair and Symbicort, are not recommended as first line agents. Asmanex is the first and only FDA approved inhaled corticosteroid indicated for once daily maintenance therapy. This means that patient compliance may increase due to the dosing use. Asmanex Twistinhaler has a unique delivery device. The patient needs to twist the device and inhale. It does not contain a propellant, and the patient does not need to coordinate actuation and inhalation. Asmanex recently received a pediatric indication down to the age of 4 years. The dosing for the pediatric population is one puff of 110mcg once daily in the evening. For the adult population, Asmanex is one puff of 220mcg once daily in the evening. This may increase the dosing compliance. Asmanex has an unsurpassed clinical efficacy and safety profile. Asmanex binding affinity for the glucocorticoid receptors is 7 times that of triamcinolone, 5 times that of budesonide, and 1.5 times that of fluticasone. In an 8 week multicenter placebo-controlled double blind double dummy study with 262 patients versus Pulmicort, Asmanex was found to improve FEV1's by 9% compared to just 2% with Pulmicots. For a 12-week multicenter double blind placebo-controlled trial with 400 previously treated patients with mild to moderate persistent asthma, Asmanex was found to be superior to placebo with respect to changes in FEV1. Additionally, Asmanex patients experienced 83% less nighttime awakenings compared to those taking placebo. Asmanex side effect profile is similar to placebo, with the most common side-effects being headaches, pharyngitis, allergic rhinitis, and upper respiratory tract infections. Asmanex mean absolute systemic bioavailability is less that 1%, which is the least amount of the inhaled corticosteroids. This may mean that the systemic side effects of Asmanex may be less due to this low systemic bioavailability. In summary, in patients 4 years and older, Asmanex has demonstrated unsurpassed clinical efficacy, tolerability, and ease of use. The Committee is asked to consider the scientific evidence presented on Asmanex and add Asmanex to the PDL.

Steven Zhang, M.D., Ph. D., from Abbott addressed the Committee. To answer the earlier question, there is no generic for all of these drugs, because all of the generic makers will have to re-run the clinical trials for new devices. Asmacort from Abbott is triamcinolone acetonide. Each canister can hold up to 240 inhalations. In the multiple randomized controlled clinical trials, Azmacort significantly improved lung function and reduced both night time and day time symptoms by over 40%. Triamcinolone can significantly reduce the need for rescue medications, such as albuterol. In the newly released NHLI guidelines, inhaled corticosteroids are recommended as the preferred agent in the first-line treatment of mild persistent asthma. The ICS, such as Azmacort, provided significant benefit to reduce the airway inflamation, as well as possibly the remodeling of the airway. More importantly, the new national guidelines recommend the use of a spacer with the inhaled corticosteroids. The spacers are intended to trap the large particles emitted from the inhaler, and thus improve the lung deposition and reduce the oropharyngial deposition of the inhaled corticosteroids. Azmacort is the only actively promoted product on the market with a built-in spacer. This eliminates the need and compliance problems associated with the spacer. According to some studies, only 50% of patients receive a prescription for a spacer, and 75% of those patients did not get those prescriptions filled due to cost or inconvenience. Azmacort has a pediatric indication, which is important for the state of Utah, where 40% of the asthmatic population is children. There have been over 5.3 million prescriptions already filled. The Committee is asked to consider Azmacort.

Karen Gunning asked the average dose in the number of puffs per dose for Azmacort. The average person needs to take 2 puffs 3-4 times per day for adults or 3-4 puffs 2 times per day. The lung deposition per puff is lower due to the spacer.

Doug Ethel, Pharm D. Of GSK addressed the Committee. There are two dosing forms of Flovent - a dried powder inhaler and a HFA MDI. There are 3 different strengths of HFA MDI, and a spacer can be attached. The discus is used without the spacer. Flovent is indicated down to age 4. Since Advair is on the PDL as the next level of care, there is a continuity of care with fluticasone as a first-line inhaler for low dose corticosteroid therapy. This way, the steroid stays the same when the patient is moved to the next treatment regimen.

Maria Papayoti, Ph. D. from AstraZeneca addressed the Committee. Symbicort is also on the PDL as combination therapy for moderate to severe asthmatic patients. It actually can be utilized as first line therapy for those patients that are moderate to severe. Symbicort has the inhaled corticosteroid of budesonide, which is in the family of Symbicort and Pulmicort. AstraZeneca has Pulmicort Respules and Pulmicort Flexhaler. Pulmicort Respules is a budesonide inhalation suspension. It is the only FDA-approved inhaled corticosteroid approved for children as young as 1 year old. It is indicated for children up to 8 years old. It is the only nebulized inhaled corticosteroid available in the U.S. Nebulization is a good way to treat the very young children. There are no FDA approved generic formulations currently available. The efficacy and safety of Pulmicort Respules has been established in clinical trials involving over 1,000 young children. Follow-up studies for one year confirm the lack of HPA suppression with Pulmicort Respules in young children. Pulmicort Respules has also been administered for up to 3 years in very young children with asthma without seeing significant side effects. Pulmicort Flexhaler is a dry powder inhaler. Its efficacy and safety has been established in patients from 6-80 years old. It is indicated for children as young as 6, but it does not go down to 4 because it is a dry powder inhaler. Budesonide is the molecule that is found in Pulmicort Respules, Pulmicort Flexhaler, and Symbicort. The budesonide molecule is pregnancy category B. All the other inhaled corticosteroids are category C. There is human data available showing that over 2,500 infants born to mothers that utilized budesonide during early pregnancy and no difference between the mothers that were treated and the general population was found when it came to congenital malformations of children. Budesonide has been utilized in longterm periods of up to 13 years in children. No differences in growth velocity were found in the treated children. There was also another study conducted in the U.S. in children 5-12 years old. Children were treated for up to 4 years and had similar growth velocity by the end of the 4 years. Budesonide should only be used in pregnant women only if it is necessary. When children are treated with any inhaled corticosteroid, growth velocity needs to be monitored.

Karen Gunning asked if the nebulizer solution only has a pediatric indication. The nebulizer solution is only indicated for patients aged 1-8. Studies have been conducted in older patients, but it is off-label.

Dr. Ward read a letter from Kathleen Hogan, N.P. The P&T Committee was asked to maintain Azmacort on the PDL. It is an effective treatment option. The built-in spacer allows patients to more effectively manage their disease.

Dr. Beckwith was asked if the efficacy of spacers was considered in the Oregon document. There was no discussion of spacers, possibly because of the way that the studies that were used were set up.

Likewise, the Oregon document attempted to evaluate compliance based on the number of puffs per day. Because of the way that the studies were designed with double dummy, it was not possible to assess this.

Dr. Miller stated that it is necessary to maintain access to Pulmicort Respules up to age 3 for the pediatric population. He also clarified that Medicaid does pay for spacers for clients. Pediatricians have been advised that it is necessary for children to have spacers, because they decrease the potential side effects in growing children. Dr. Beckwith pointed out that the Azmacort product will be changing by the end of 2009, due to the propellant. The new product may not have a spacer.

Karen Gunning stated that the nebulizer solution must be included, because it is the only nebulized formulation and it is the only one approved down to age 1. She stated that it would be an interesting DUR matter to check and see how much of the Pulmicort respule use is in adults. Also, the Committee should consider how many puffs per day need to be used for a product, because it probably impacts compliance. Access to items that require less puffs per day should be maintained to improve control of asthma in Utah.

The Committee asked if any studies were conducted to determine ease of use for patients with physical deformities or conditions such as cerebral palsy. There were no such studies in the Oregon document. The manufacturers did not have any trials like this to address the question.

Tim Morley stated that the Transformation Grant is now doing an in-depth analysis of asthma control in the Medicaid population in Utah.

The Committee asked if there are any step edit capabilities for asthma drugs. The only way to manage this would be through a PA, which is DUR purview. Karen Gunning stated that it is also difficult to determine whether leukotriene agents are being utilized appropriately, due to their use outside of asthma.

Lisa Hulbert stated that the Transformation Grant has already analyzed claims data for pediatric asthma clients, looking at medical and pharmacy claims data. They are still trying to correlate hospitalization and medical encounter data with pharmacy claims.

Dr. Wohleb asked if there are quantity limits on inhalers. The monthly quantity limits on the inhalers are one more than the amount necessary for a one month supply.

The Committee pointed out that there is a variability in the FDA approved ages for the inhaled corticosteroids. From a medical legal standpoint, it is important to approve an inhaler that is approved down to age 4.

Dr. Beckwith announced some changes to FDA approved ages that have occurred since the publication of the Oregon document. Qvar is approved for age 5 and older, Pulmicort flexhaler age 6 and up, Pulmicort Respules age 1-8, Aerobid and Aerobid M ages 6 and up, Flovent HFA age 4 and up, Flovent Discus age 4 and up, Asmanex age 4 and up, and Azmacort age 6 and up.

Karen Gunning moved that the Committee find that all orally inhaled corticosteroids have equal safety and efficacy. Kort DeLost seconded the motion. The motion passed with

unanimous votes from Kort DeLost, Karen Gunning, David Harris, Duane Parke, Raymond Ward, and Jerome Wohleb.

Karen Gunning moved that the nebulized product must be included as preferred. Dr. Wohleb seconded the motion. The motion passed with unanimous votes from Kort DeLost, Karen Gunning, David Harris, Duane Parke, Raymond Ward, and Jerome Wohleb.

Karen Gunning moved to include at least one of either fluticasone or mometasone. Kort DeLost seconded the motion.

Dr. Miller wanted to reopen the motion for discussion. He is not sure that the dry powder inhaler may not be as safe as a MDI with a spacer. Karen stated that there may be differences between CFC and HFA MDIs. All of the studies that are available have used the CFC inhalers. Medicaid would not need to choose either a dry powder inhaler or an MDI - she is recommending that at least one should be included. Medicaid could choose to include all of these products, but there should be at least one product with a low number of inhalations per day on the list. The motion passed with unanimous votes from Kort DeLost, Karen Gunning, David Harris, Duane Parke, Raymond Ward, and Jerome Wohleb.

Dr. Wohleb asked to see asthma guidelines when they are available.

The Committee felt that it may be helpful to know which clients taking leukotriene agents are also on beta agonists, and which clients taking leukotriene agents are also taking inhaled corticosteroids. The Committee asked that this information be fractionated by age.

Next meeting set for June 20, 2008.

Meeting adjourned.

Minutes prepared by Jennifer Zeleny